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Evaluation of Clinicopathological Features and Associated Conditions in Erythema Annulare Centrifugum: A Retrospective Observational Analysis of 63 Patients

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ABSTRACT

Introduction: Erythema annulare centrifugum (EAC) is a rare reactive disease that typically presents as annular or polycyclic erythematous lesions. There are few studies about EAC in the literature; therefore, data on the pathogenesis of the disease are limited.

Objectives: We aimed to examine the demographic, clinical, pathological characteristics and associated conditions of the patients with EAC.

Methods: We analyzed records of the patients with EAC who admitted to our clinic in the last four years retrospectively.

Results: A total of 63 patients, 39 women and 24 men, were included in our study. The mean age of the patients was 47.8±11.2 years. The mean disease duration was 15.54±12 months. The trunk and thigh were the most commonly involved sites (49%, 33%). Associated conditions were identified in 52.3% of the patients. Infections (N = 16), malignancies (N = 6), rheumatic diseases (n=4) and drugs (n=4) were the most common precipitating factors respectively. The most common infections were superficial fungal infections and Helicobacter pylori infection. Histopathologically, 10 patients had deep type and 53 patients had superficial type EAC. We determined that the disease duration from the onset of the disease was longer (12.3 versus 16.2 months) and the number of attacks (1.2 versus 2.8 attacks) was higher in the superficial type when compared to the deep type (P = 0.042, P = 0.038).

Conclusions: In our study, infections, malignancies and rheumatic diseases were among the most common etiologic factors. We would also like to draw attention to Helicobacter pylori infection as a precipitating factor which may be a novel finding.

Introduction

Erythema annulare centrifugum (EAC) is a slowly progressive eruption characterized by annular or polycyclic erythematous papules and plaques [1]. EAC is considered a type 4 hypersensitivity reaction to an antigenic stimulus [2]. The term EAC was first used by Jean Darier in 1916 [3]. Darier referred to EAC also by a synonym "érythème papulo-circiné migrateur et chronique" [3]. There are few studies on EAC in the literature which are retrospective studies with small number of patients [4-6]. The exact prevalence is unknown [1]. EAC is seen in two clinical forms, superficial and deep [2,7]. In both forms, the lesions start as a hard erythematous papule with centrifugal spread, which begins to heal from the center. The superficial type appears as erythematous, non-indurated plaques. On the inner side of the advancing margin, trailing scale is typical. In the deep type, there is typically no scale, and the advancing borders are raised and indurated. Lesions may sometimes persist for weeks and months, regressing and disappearing without leaving a scar [2,7]. Paraneoplastic EAC associated with malignancy is called PEACE (paraneoplastic erythema annulare centrifugum eruption) [8]. EAC may start years before, simultaneously or later than malignancy [9]. The first approach in the treatment of EAC is to treat the underlying disease if one is detected. Since it usually regresses spontaneously without treatment and is largely asymptomatic, it can be followed up without treatment in mild cases [1,10]. Some authorities recommend empirical use of antibiotics and antifungal agents even if the cause cannot be identified. Although systemic steroids provide clinical remission, they are not preferred since the findings tend to recur after discontinuation of the drug [10,11]. Local tacrolimus, calcipotriol, oral metronidazole, subcutaneous interferon and apremilast were reported to be beneficial in some patients [12-15]. However, it has been reported that the treatments did not change the chronic and recurrent course of the disease [6].

The histopathology of EAC varies according to its type. In the superficial type nonspecific findings such as mild spongiosis, microvesiculation, focal parakeratosis, epidermal hyperplasia, minimal superficial perivascular lymphohistiocytic infiltration are seen. Furthermore, edema of the papillary dermis is more common in the superficial type [1,4]. In the deep form, epidermal changes are not prominent and mononuclear cell infiltration with dense perivascular aggregation is evident in the mid and lower dermis which leads to elevated and more indurated lesions in the deep form of EAC clinically [1,4]. In addition, inflammatory cells typically accumulate densely around the vessels in a so-called "sleeve" fashion [1,4]. This typical infiltration may be considered as a marker for the differentiation of EAC from other figurate erythemas. Since fibrin extravasation is not expected in EAC, it can be considered as pseudovasculitis [1,4].

Objectives

The aim of our study was to evaluate the demographic, clinical and histopathologic characteristics of patients with EAC and to examine the associated diseases.

Methods

Our study was designed as a retrospective study in a tertiary referral hospital. We analyzed data of the patients over the age of 18 years who were followed up with a diagnosis of EAC between January 2019 and January 2023. We stipulated a clinicopathologic correlation in our study to exclude other annular erythemas resembling EAC. Ethics committee approval numbered E1-23-3287 was obtained before the study (08.02.2023). Statistical analysis calculations were made with Statistical Package for Social Sciences (SPSS) version 24.0 for Windows program. Continuous variables (age, duration of disease) are expressed as mean and standard deviation, while categorical variables (localizations of lesions, number of attacks, histopathological subtype, associated conditions, concomitant diseases, treatments received) are expressed as number and percentage. Chi-Square test statistics was used to compare categorical measurements. Statistical significance level was accepted as 0.05 in all tests.

Results

We included a total of 63 patients, 39 (62%) females and 24 (38%) males, aged between 19 and 84 years in our study. We had excluded five patients with missing or incongruous histopathological data on the eve of the study. The mean age of the patients was 47.8±11.2 years. The duration of disease ranged from 1 week to 10 years with a mean of 15.54±12 months. In 19 patients, the duration of disease was longer than 1 year and the disease persisted for an average of 45.8 months. Trunk, thighs and arms were the most frequently affected sites (Figures 1 and 2). Localizations of the lesions are shown in Table 1. Involvement in multiple localizations was observed in eight patients. The number of attacks of the patients varied between 1-20 attacks. Multiple attacks developed in 43% (N = 27) of the patients and it was the first attack in 57% (N = 36). In patients with multiple episodes, the episodes recurred in an average of 9.1 months. Histopathologically, 10 (15.9%) and 53 (84.1%) patients had findings compatible with deep (Figures 3 and 4) and superficial type EAC, respectively. It was consistent with clinical deep and superficial types. We evaluated all patients diagnosed with EAC in our study in terms of underlying diseases. Factors that may be involved in the etiology were found in 52.3% of the patients. Associated conditions are shown in Table 2. Eight patients had fungal infections (tinea pedis

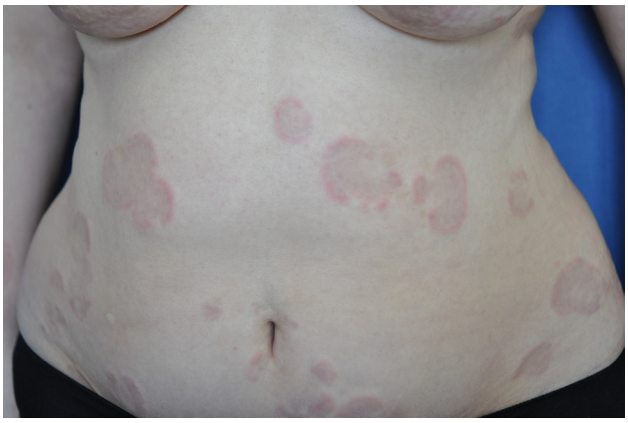

Figure 1. Our patient with deep type of EAC. Non-scaly erythematous annular plaques with central clearence.

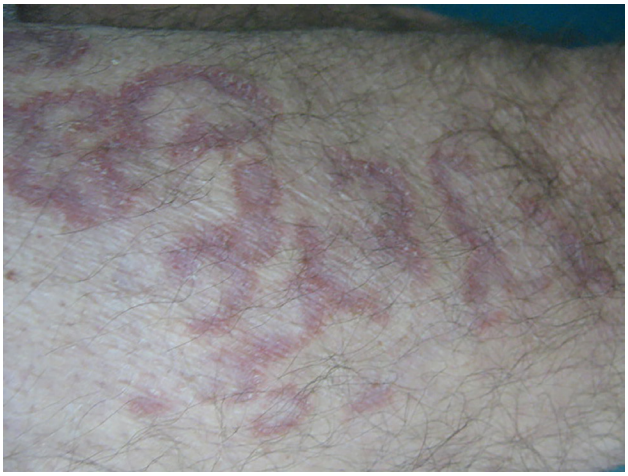

Figure 2. Our patient with superficial EAC. Erythematous and annular plaques with a trailing scale.

Table 1. Localizations of the lesions in the patients.

Localizations of the lesions	N (%)
Trunk	31 (49.2)
Thigh	21 (33.3)
Arm	14 (22.2)
Gluteal area	7 (11.1)
Neck	1 (1.6)

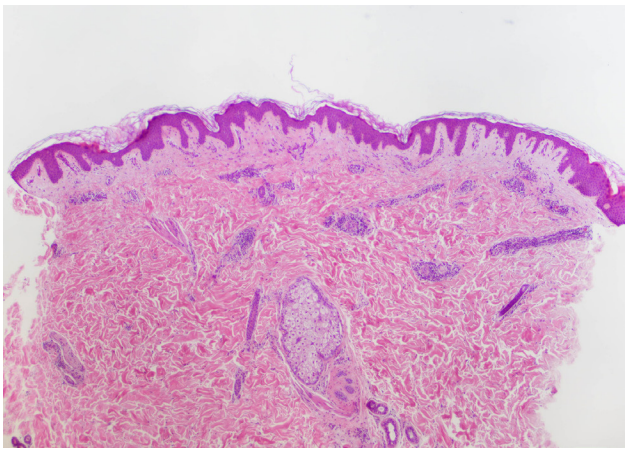

Figure 3. Our patient with histopathologically deep type of EAC (who was also clinically consistent with deep type of EAC). Tight perivascular mononuclear cellular infiltrate in both upper and lower dermis without prominent epidermal changes and edema of the papillary dermis (H&E, X40). From the archive of Dr. Nuran Süngü, Ankara City Hospital, Department of Pathology.

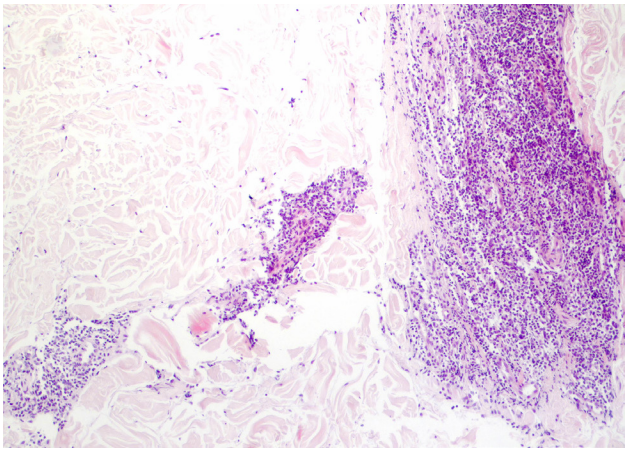

Figure 4. Perivascular mononuclear infiltrate, tightly adherent to vascular plexus in "coat sleeve pattern" (H&E, X100). From the archive of Dr. Nuran Süngü, Ankara City Hospital, Department of Pathology.

and/or tinea unguium in 7 patients, vaginal candidiasis in 1 patient), 4 patients had gastritis and Helicobacter pylori infection. There was one case each of urinary tract infection, upper respiratory tract infection, Coronavirus disease 2019 (COVID-19), HIV infection and pregnancy. Four patients had a history of drug use (analgesics, oral contraceptives, antibiotics, escitalopram, 1 case of each of them). Two patients had Hashimoto thyroiditis. Malignancy was detected in 6 patients (gastric cancer: 1, cervical cancer: 1, prostate cancer: 2, breast cancer: 1, thyroid cancer: 1). The diagnosis of malignancy was made before the onset of EAC in 5 of the patients while in one patient it was made concurrently with EAC. Of these patients, 3 were in remission or cured, while in 3 patients the disease was active and they were receiving chemotherapy. Four patients were diagnosed with rheumatic diseases (juvenile rheumatoid arthritis, palindromic rheumatism, rheumatoid arthritis, granulomatosis with polyangiitis, 1 case of each of them). The most common concomitant diseases were gastritis (N = 10), diabetes (N = 7), hypothyroidism (N = 6), malignancy (N = 6) and rheumatic disease (N = 4) respectively. Concomitant diseases are shown in Table 3. In our study, when superficial and deep types were compared based on the clinical and histological classification,

Table 2. Associated conditions which were blamed for triggering erythema annulare centrifugum in the patients.

Associated conditions, N (%)	N
Infections, 16 (25.3)	tinea pedis/unguium: 7 vaginal candidiasis: 1 Helicobacter pylori infection: 4 urinary tract infection:1 upper respiratory tract infection: 1 COVID-19:1 HIV infection:1
Malignancies, 6 (9.5)	prostate cancer:2 gastric cancer:1 cervix cancer:1 breast cancer:1 thyroid cancer:1
Rheumatic diseases, 4 (6.3)	juvenile romatoid arthritis:1 romatoid arthritis:1 romatoid arthritis:1 granulomatosis with polyangiitis:1
Medications, 4 (6.3)	oral contraceptives:1 analgesics:1 antibiotics:1 escitalopram:1
Endocrinopathies, 2(3.1)	Hashimoto thyroidit:2
Other, 1(1.5)	pregnancy:1

Table 3. Concomitant diseases in the patients.

Concomitant diseases	N
Gastritis, dyspepsia	10
Esophagitis	2
Diabetes	7
Hypothyroidism	6
Malignancy	6
Rheumatic disease	4
Hypertension	3
Asthma, allergic rhinitis	3
Fibromyalgia, depression	2
Chronic renal impairment	1
HIV infection	1
Hepatitis B carrier	1

no difference was found in terms of age, gender, lesion localization, triggering factors and comorbidities (P > 0.05), whereas the total duration of the disease from the onset of the disease was longer (12.3 versus 16.2 months) and the number of attacks (1.2 versus 2.8 attacks) was higher in the superficial type compared to the deep type (P = 0.042, P = 0.038).

Table 4. Treatments received by the patients.

Treatments	N (%)
Topical corticosteroids	30 (47.6)
Topical calcineurin inhibitors	8 (12.6)
Terbinafine	6 (9.5)
Calcipotriol	4 (6.3)
Azithromycin	3 (4.7)
Systemic steroid	2 (3.2)
Dapsone	1 (1.6)
Fluconazole	1 (1.6)
None	17 (26.9)

Topical steroid (N = 30), topical calcineurin inhibitor (N = 8), terbinafine (N = 6) and calcipotriol (N = 4) were the most commonly received treatments by our patients (Table 4). We determined that 26.9% (N = 17) of the patients did not receive any treatment. The lesions resolved in some of these patients while waiting for the results of skin biopsy or the laboratory tests made for revealing precipitating factors. Also, some of the patients did not apply their treatments. Treatment responses could not be evaluated in our study because of the self-healing tendency of EAC and dropout of some patients from treatment.

Conclusions

In our study, 62% of the patients were female and 38% were male. The mean age of the patients in our study was 47.8±11.2 years and the mean disease duration was 15.54±12 months. In a study by Kim et al evaluating the demographic and clinical characteristics of 39 patients with EAC, 64% of the patients were female and 36% were male [5]. In another study, 24 (36%) of 66 patients with EAC were male and 42 (64%) were female. In the same study, the mean age was 39.7 years and the mean disease duration was 2.8 years [6]. The mean age and gender distribution in these studies were similar to our study.

We observed that the most commonly involved areas in our patients were the trunk and thigh, respectively. In the study by Kim et al the lower extremities, especially the thigh, were reported as the most commonly affected region [6]. In the study by Weyers et al it was found that the main predilection site was the trunk in both types similar to our study, whereas the extremities and buttocks were more commonly involved in the superficial type and the face and neck in the deep type [4]. In our study, the number of attacks varied between 1-20 attacks and the attacks recurred in a mean of 9.1 months. In the study by Kim et al the mean duration of persistent lesion was found to be 4.7 months [5].

In our study, 15.9% and 84.1% of the patients had findings compatible with deep and superficial type EAC,

respectively. Similar to our study, 82.1% of the cases were evaluated as superficial type and 17.9% as deep type in the study by Kim et al [5]. In another study, it was also found that 78% of the patients with available data had superficial type EAS and 22% had deep type EAC [6].

We identified associated conditions in 52.3% of the patients in our study, while we evaluated that 47.6% were idiopathic. In the study of Kim et al 33.3% of the patients were found to have potentially related factors (cutaneous fungal infections, pregnancy, malignancy, autoimmune diseases and drugs) [5]. In the study by Weyers et al infections, rheumatoid arthritis, thrombocythemia, malignancies, allergic asthma and drug reactions were blamed in 36 percent of the patients [4]. In the study by Kim et al 72% of patients had comorbidities. Associated diseases were categorized as cutaneous fungal infections (48%), other skin diseases (18%), malignancies (13%) and other systemic diseases (21%) [6]. Due to the paucity of data in the literature on EAC, the underlying causes are not fully known and are of great interest. The associations detected after the diagnosis of the disease have been generally reported as cases to date, and a clear relationship is usually not established. In our study, the most frequently associated conditions with EAC were infections, malignancies, rheumatologic diseases and drugs, respectively. This result was similar to aforementioned studies. Also the most common infection was superficial fungal infections in concordance with previous studies. Helicobacter pylori infection was the second most common infection detected in our study. Since our study allowed a 4-year follow-up of medical records, we observed that most of our patients had complaints of dyspepsia and heartburn. They were evaluated for gastritis in internal medicine and gastroenterology departments close to or immediately after the onset of the disease, and endoscopic examinations were performed in some patients. As a matter of fact, gastritis was the most common disease found in the patients history. Indeed we discovered that EAC disappeared after antibiotic treatment for Helicobacter pylori infection in our patients and did not recur as far as we could follow up. We think that there may be a causal relationship between EAC and Helicobacter pylori infection, which we observed in our study.

In our study, all of the patients with associated malignancy had solid tumors. In a case series of 40 patients followed up with a diagnosis of PEACE, association with lymphoproliferative diseases (most frequently leukemia and lymphoma) was observed in 62.5% of the patients and with solid tumors in 37.5% [8]. In the study of Kim et al 2 of 39 patients had thyroid cancer [5]. In the study by Weyers et al the number of patients with associated malignancy was 6 (13.33% of those with an associated disease) and the disease was active in only one of these patients [4]. In a patient diagnosed with breast cancer EAC was associated with disease activation and lymph node metastasis was found [9]. In that case, it was emphasized that if EAC occurred due to an underlying disease, EAC may be correlated with exacerbations of this disease [9]. The possible activation of cancer was also investigated in our patients who were in remission but no recurrence of malignancy was detected. We had 2 cases of Hashimoto thyroiditis. A case that started 3 months before Hashimoto thyroiditis and was associated with Hashimoto thyroiditis has been reported previously [16]. We had one case associated with pregnancy. Similar to our case, EAC associated with pregnancy has been reported. In that patient, EAC developed in pregnancy and completely disappeared 1 week after delivery without treatment and did not recur in 1-year follow-up [17]. Although 11.1% of the patients in our study had a history of diabetes mellitus, no direct association with the disease was established and no such association has been found in the literature.

When we compared superficial and deep types based on both clinical and histological classification, we found that the total disease duration from the onset of the disease was longer and the number of attacks was higher in the superficial type compared to the deep type. In the study by Kim et al the detection of higher recurrence rate in the superficial type supports our findings [5]; however, it should be kept in mind that the number of deep-type EAC cases was very low in both studies.

The most important limitations of our study are the small number of patients and the retrospective design of our study which led to missing data about treatment responses. There is an obligatory overlap between some of associated conditions and concomitant diseases in our study. Associated condition may be a concomitant disease and vice versa is also possible. We favored to group associated conditions according to priorly defined causes of EAC in the literature. Four of the patients with gastritis had also Helicobacter pylori infection. After Helicobacter pylori eradication EAC lesions regressed, so we blamed it as a triggering factor and these four patients were included in both of associated conditions/infections and concomitant diseases/gastritis category. Similarly two patients with Hashimoto thyroiditis were diagnosed concurrently with EAC and they were included in both of the categories as associated conditions/endocrinopathies and concomitant diseases/hypothyroidism. Remaining four patients with hypothyroidism suffered from the disease for many years and they were stable under treatment. We could not establish a cause-and-effect relationship and put them only in concomitant diseases group.

We described the demographic and clinical characteristics of patients with EAC in our study. We would like to point out that the association with Helicobacter pylori infection, which we observed in our study may be significant. We also found that the superficial type had a longer disease

duration and a higher number of attacks compared to the deep type. However, all the data we have obtained should be confirmed by future studies with a larger number of patients.

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